Progress in Cardiovascular Diseases: Cognitive Function in Essential Hypertension

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Essential hypertension has rather recently become recognized as a major factor in the development of the 2 main types of dementia, that is, no longer merely vascular dementia but Alzheimer disease as well. The relationship between high blood pressure (BP) and the dementias is quite a complicated one, given a wide variability in temporal courses. The interval between the respective manifestations of hypertension and cognitive deterioration may vary from a few years to several decades. Moreover, temporal relationships may be obscured because of the observation that BP tends to fall in the face of imminent Alzheimer disease. Although the cause-and-effect sequence of this relationship has not been established, it may suggest that a low BP in this phase of life could be equally harmful as hypertension in the preceding period. Individual monitoring of BP and drug titration in the hypertensive elderly may well become mandatory in the highest age group. The question whether some antihypertensive drug categories might act more effectively in preventing cognitive deterioration than others, irrespective of their antihypertensive potential, remains. A modest meta-analysis on our part seems to suggest that suppression of the renin-angiotensin-aldosterone system (RAAS) would fail to offer such protection, in contrast to certain dihydropyridine (DHP) calcium-channel blockers. Unfortunately, recently published comparative prospective megatrials (Anti-hypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial and Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) failed to carry any record on the mental status of the study populations, thereby missing a golden opportunity to resolve the above issue. Consequently, there remains an urgent need for further blinded long-term comparative hypertension trials, including follow-up evaluation of cognitive functions in relation to the course of BP.

Cognitive deterioration and its end point overt dementia are, in brief, to be characterized by progressive memory loss, disorientation in time and space, loss of autonomy, and ultimately, depersonalisation/alienation.

The dementia syndrome by tradition used to be specified into 2 main prototypes: degenerative dementia or Alzheimer disease vs vascular dementia. Despite a vast and ongoing literature on differential features between the 2 forms, the overriding importance of such discriminating characteristics is now moving to the background in the face of epidemiologically oriented research. As Hofman et al[1] in Rotterdam have shown, the 2 subtypes share atherosclerosis as a major background factor, partly dependent on the presence or absence of the apolipoprotein E genotype. The atherosclerotic component of Alzheimer disease has also been stressed by Casserly and Topol.[2]

From another angle, a collaborative neuropathological study under the auspices of the Medical Research Council (UK) confirmed a considerable overlap between the microscopic substrates of degenerative and vascular dementia.[3]

Epidemiology of Dementias at Large

Traditionally, both subtypes of dementia are associated with the aging process and, hence, increase pari passu with the longevity of humankind, as estimated in the Europe and the United States. In the western world, some 10 years ago, the prevalence of memory impairment in the

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older population was already estimated to be 17% to 34%,[4-7] and overt dementia (80% of the Alzheimer type) affected 3.6% to 10.3% of the population older than 65 years.[8,9]

It is estimated that the incidence of dementia exponentially increases with age with rates of 5 to 10 cases per 1000 person-years at 70 years and older to 20 to 40 cases per 1000 person-years at 80 years.[10] Hence, given the current worldwide demographical transition from high to low rates of birth and death, dementia is bound to grow into one of the principal causes of disability and reduced general quality of life in the community at large.

A major concern is that medical treatment of established dementia, so far, has shown only marginal benefit, without any promise of cost-effectiveness.[11,12]

This reinforces the need for focusing on the possibility of prophylactic measures to be derived from potential cofactors involved in the pathogenesis of degenerative and vascular dementias. Unfortunately most of those are hardly, if at all, amenable to social or medical interference (Table 1). It appears that the major preventable factor is liaised with hypertension and its sequelae or associated metabolic derangements.

Table 1. Factors Involved in Cognitive Impairment and Dementia

- Aging
- Family history
- Apolipoprotein E4 allele
- Sex (female > male)
- Vascular risk factors and damage (hypertension, diabetes, and stroke)
- Depression
- Poor educational level
- Sedentary lifestyle
- Social disengagement

Hypertension and Dementia

Although hypertension has long been recognized to play a role in the pathogenesis of vascular dementia, its identification as an equipotent risk factor in Alzheimer disease had to await the final decade of the past century. This has mainly been due to the lengthy lag phase between the clinical diagnoses of hypertension and cognitive deterioration, thus preventing consistent correlations between the 2 on a cross-sectional (contemporary) basis. The moot results of such comparisons have been extensively reported elsewhere.[13,14] The extent of the apparent phase difference between the 2 conditions is due to the insidious nature of hypertensive target organ damage. For decades, histologic lesions, such as neurofibrillary tangles or an accelerated rate of neuronal atrophy in the medial temporal lobe of the brain,[15,16] may precede overt dementia.

Because cross-sectional studies obviously lack the potency to disclose an ad hoc intimate relationship between blood pressure (BP) and cognitive deterioration, longitudinal studies were required to provide proper evidence pro or contra a causative long-term relationship.

Overall, such follow-up studies have revealed a high BP to be a graded and continuous risk factor in the pathogenesis of both vascular and degenerative dementias in the course of the decade(s) after midlife.

In the Framingham study,[16] BP levels of participants 55 to 88 years of age were followed up and averaged more than 5 biennial examinations in an era (1956-1964) when most hypertensive patients stayed untreated. In the period 1976 to 1978, in 1038 untreated survivors, the composite cognitive score with separate measures of attention and memory appeared to be inversely correlated with systolic and diastolic BP at baseline.[17]

The substance of this finding was confirmed in 2 studies from Sweden, Gothenburgh[18] and Uppsala,[19] and by the Honolulu-Asia Study,[20] with follow-up periods of 15, 20, and 25 years, respectively.

Although the above studies basically established a positive relation between baseline BP starting at any age and the risk of cognitive impairment and overt dementia in the subsequent age range, this turned out to be less clear in subjects receiving antihypertensive treatment in the interim,[19] as could be expected.

A variant course of late-life events was discovered by Skoog et al[18] in their meticulous follow-up of hypertensive patients 70 years and older. They examined the relationship between BP and dementia starting with nondemented patients at 70 years of age and following them up

at 5-year intervals up to 85 years of age. In this observation period, patients prone to developing degenerative dementia later on had higher systolic and diastolic BPs than the others but paradoxically exhibited a fall in BP in the years before the onset of dementia. White matter lesions on magnetic resonance imaging appeared to predispose to this phenomenon.[18]

This paradoxical decline in BP in patients at increased risk of dementia is still to be explained. Physical inactivity in those blemished by advancing mental deterioration may be a substantial factor. Skoog[21] proposed another hypothesis in that failure to maintain usual BP at this stage might well be an expression of Alzheimer-type lesions in prefrontal autonomic ganglia resulting in central dysregulation of BP control. Orthostatic or postprandial dips in BP, pari passu with episodes of impaired cerebrovascular blood flow, might indeed contribute to further cerebrocellular damage.[22]

Whatever the mechanism of this rather ominous BP decline, in practice, it should require careful titration/adjustment of ongoing antihypertensive medication in the very elderly. The latter aspect will be discussed later on.

At the early part of the age spectrum, a recent observation revealed a comparable seemingly paradoxical development. Although it has been commonly accepted that the incidence of dementia exponentially increases with age with rates from 5 to 10 cases per 1000 person-years at 70 years and older to 20 to 40 cases at 80 years,[10] it now seems that recognition of cognitive decline should no longer be limited to hypertension in the elderly. In the Maine-Syracuse Longitudinal Study of Hypertension, Elias et al[23] followed up subjects in 2 age groups (18-46 and 47-83 years) for (potentially) up to 20 years. In a sophisticated 2-step growth curve analysis, baseline BPs, categorized according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[24] and various cognitive performance ratings, were evaluated in both age groups. It appeared that the young (in a decline in visualization/fluid abilities) were equally vulnerable in relation to BP increments as their older counterpart. This finding should serve as, perhaps, an even stronger stimulus to contain hypertension in its early stage than the avoidance of more distant mental sequelae.

Role of White Matter Lesions

White matter lesions on computed tomography or magnetic resonance imaging are "endemic" among the elderly.[25] Still, their absence or presence may be clinically important, as already alluded to above in the study by Skoog et al.[18] The analysis/calibration of white matter lesions, particularly regarding cognitive impairment in vascular cerebral disorders, is being developed into a refined art,[26] which may, in due time, hopefully be correlated with psychometric findings.

The role of hypertension in generating progressive white matter lesions, which correspond to ischemic destruction of deep neuronal axons, often with advanced microangiopathy (leading to focal infarcts as forerunners to stroke and/or neurodegenerative disorders), has long been ignored. This episode of ignorance/neglect has come to an end by virtue of a range of prospective cohort studies wherein measurement of BP at entry antedated magnetic resonance brain imaging by 5 to 20 years and was repeated at the time of the scans.

After adjustment for eventual confounders, the prevalence and incidence of white matter lesions augmented with high BP.[27,28] This pattern was subsequently roughly confirmed by the Cardiovascular Determinants of Dementia Study (CASCADE) Consortium in which the above investigators closed ranks with those from 7 other European countries.[29] The association between white matter lesions and BP was particularly strong in subjects with uncontrolled hypertension. It was graded and continuous for systolic pressure but J-shaped for diastolic pressure. The consortium speculated about various explanations that might underlie the latter aberrant relationship, but in our view, they missed the most obvious angle.[29] With aging, systolic BP tends to become the major cardiovascular risk factor. On the contrary, a decline in diastolic BP, in the same late course of aging reflects the same arteriosclerotic process as a marker of loss of arterial compliance in its own right. As a matter of fact, the cardiovascular risk of an increasing systolic BP in the elderly has been shown to be proportionally reinforced by the presence of progressively reduced diastolic pressures.[30]

Observational Studies on the Effects of Antihypertensive Treatment on Cognitive Decline

Given the successful effects of antihypertensive medication in containing stroke rates in elderly hypertensive patients,[31-36] one could reasonably hope for analogous effects regarding the prevention of cognitive decline by protecting against cerebral microvascular damage as one of the substrate constituents of vascular—as well as degenerative—dementia.

A range of observational studies relating hypertension with cognitive malfunctioning incorporated the influence of concurrent antihypertensive medications.

In the Kungsholmen Project from Sweden[31] 1301 hypertensive patients 75 years and older were followed up for an average of 3 years. Cognitive functions were assessed using the Mini-Mental State Examination (MMSE) as well as additional psychometric criteria. At the end of the follow-up period, 987 subjects were still alive. In a subpopulation with a systolic BP higher than 160 mm Hg, a diastolc BP higher than 95 mm Hg, or both, 122 had received diuretic treatment. Compared with untreated subjects, the patients, thus treated, showed an adjusted relative risk for developing dementia of 0.6 (95% confidence interval [CI], 0.3-1.2). The authors felt that this outcome might indicate a potential benefit from diuretic treatment, although they recognized the flaws of this study in that the information on treatment was merely available at baseline; moreover, confounding by indication may well have biased the results.

In a further follow-up phase of the Kungsholmen project,[32] it was observed that a very low diastolic BP (<65 vs 66-90 mm Hg) was associated with an increased risk for dementia, particularly in patients on antihypertensive treatment. Conversely, a high systolic BP (>180 mm Hg) carried a similar risk, whereas low systolic pressures (140 mm Hg) appeared to be quite harmless. Apparently, a further accumulation and integration of BP data will be needed to arrive at a consensus for optimal BP titration for cognitive preservation.

In the Epidemiology of Vascular Aging study,[33] 1389 subjects 59 to 74 years of age, were recruited, including 167 hypertensive patients who were re-examined 2 and 4 years later. After 4 years, 81 hypertensive individuals had received antihypertensive treatment with various drugs (β-blockers, calcium-channel blockers [CCBs], angiotensin-converting enzyme (ACE) inhibitors, and diuretics). In untreated hypertensive patients, a correlation was observed between the level of BP and a subsequent decline in cognitive function (a decrement of >4 points on the 30-point MMSE scale). The relative risk amounted to 4.3 (95% CI, 2.3-8.0) as compared with normotensive patients. By contrast, in the treated group of hypertensive patients, the relative risk was reduced to 1.3 (95% CI, 0.3-3.9).

Recently, a retrospective analysis has been published from Indiana.[34] This was based on centralized administrative data from 1900 African Americans older than 65 years without dementia at entry. They were followed up for a period of 5 years while being treated with a variety of 7 antihypertensive drugs. During that period, 288 individuals (15%) developed overt cognitive impairment. The use of antihypertensive medications, overall, reduced the chance of developing dementia by 38% (odds ratio, 0.62; 95% CI, 0.48-0.84).

Although this looks encouraging, a corresponding analysis of reported BP measurements was inconclusive. Moreover, none of the 7 antihypertensive drug categories prescribed, when evaluated separately, achieved significant reductions in odds ratios.

The above results of antihypertensive treatment in reducing cognitive deterioration, although relatively encouraging in their own right, ought to be interpreted with skepticism because of their lack of properly matched control groups and valid comparative statistics. Moreover, a precise relation between the antihypertensive effects of different drug types and the incidence rates of cognitive deterioration/overt dementia cannot be established. There also arise caveats regarding optimal levels of achieved BPs, both systolic and diastolic, in relation to aging, as witnessed by the follow-up study by Skoog et al.[18] In particular, a sharp decline in diastolic pressure in the elderly may well prove to be counterproductive, both in systemic[30] and cerebral hemodynamic effects[32,35,36] as well as white matter lesions.[29]

A recent study from Beer Sheva, Israel, offers some further reasons for caution in that respect.[37]

The latter authors studied 495 individuals (mean age, 76.5 years) and related a range of cognitive functions to 4 groups of patients: untreated normotensive patients (n = 136; average BP, 122.6/72.6 mm Hg); successfully treated (with CCBs or ACE inhibitors) hypertensive patients (n = 74; BP, 126.8/74.5 mm Hg); untreated hypertensive patients (n = 103; BP, 152/81 mm Hg); and treated but so-called uncontrolled hypertensive patients (n = 172; BP, 158.7/85.4 mm Hg). Rather unexpectedly, the latter group scored best of all on the MMSE scale and in the cognitive domains of long-term memory and concentration. The CCBs exhibited some additionally favorable action in this regard, an aspect that will be dealt with later on.

The above results at first sight seem to deviate from current ideas about optimal (maximal) antihypertensive treatment. However, these findings reinforce the relativism arising from quoted above[18,29,30,32,35,36] in that there may be a potential hazard of "overcorrecting" BPs in subjects 70 years and older. One does not need to be clairvoyant to realize that such utterly "normalized" BP values as reported in the Beer Sheva study in elderly with long-standing hypertension may well interfere with their (chronically up-regulated) autoregulation of cerebral vascular resistance. Chronic underperfusion of the brain is quite likely to occur and thereby accentuate the process of cognitive decline.[22]

Conversely, the provocative finding that nonresponders to treatment performed better than untreated hypertensive patients is enigmatic and open to speculation (whether selective cerebral vasodilation or beneficial cerebrocellular effects). We will return to the latter issue after discussing the literature on prospective randomized trials.

Results of Long-term, Prospective, Randomized, Placebo-controlled Trials

In this regard, no specific trials have been conducted with a primary focus on prevention of cognitive deterioration per se. This kind of study had to be embedded in larger cardiovascular end point–oriented trials, if only for the obvious reason that mental disorientation cannot be studied in a somatic vacuum.

In the prospectively planned Medical Research Council (MRC) trial of treatment in older patients with hypertension,[38] subjects were properly randomized to a diuretic, β-blocker, or placebo. Psychometric tests were performed, covering a period of 54 months. In this substudy, no significant differences in test scores were detected between the actively treated groups and those assigned to placebo. Although, it should be noted that there were numerous subjects from the placebo group crossing over to active treatment, which unavoidably has confused the results with regard to the "intention-to-treat" analysis applied to the above trial.

Although the above reviewed MRC study,[38] despite elaborate psychometric assessments, unfortunately did not report on the incidence of overt dementia per se, other antihypertensive trials in the elderly focused on the incidence of dementia proper: Systolic Hypertension in the

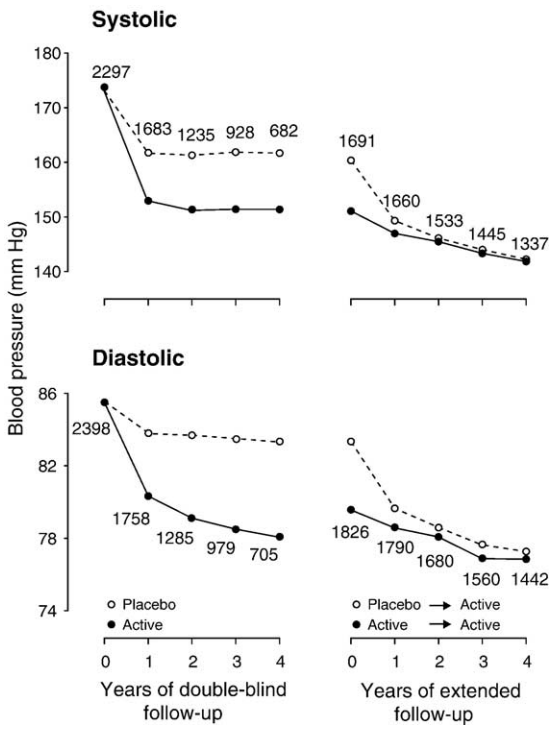

Fig 1. Syst-Eur phases 1 and 2. Systolic and diastolic BPs in patients initially assigned to placebo or active treatment. Results are separately given for 4695 patients randomized in the double-blind trial (left) and for 3517 participants subsequently enrolled in the open-label study (right). Reprinted with permission from *J Hypertens* 2004;22:847-857.

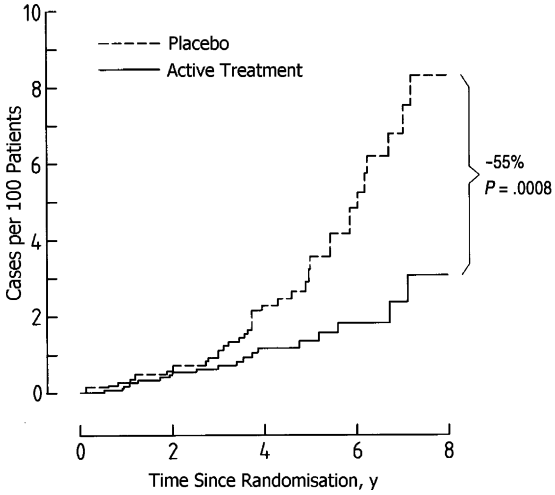

Fig 2. Incidence of dementia in the Syst-Eur trial (double-blind phase followed by open active treatment phase (intention-to-treat mode of analysis). Reprinted with permission from *Arch Intern Med* 2002;162:2046-2052.

Elderly Program,[39,40] Perindopril Protection against Recurrent Stroke Study,[41] Study on Cognition and Prognosis in the Elderly,[42] Systolic Hypertension in Europe (Syst-Eur),[43] and Syst-Eur 2.[44]

In the Systolic Hypertension in the Elderly Program trial substudy on 2034 subjects,[39] the incidence of dementia after 5 years was similar: in the placebo group, 1.9%, and in the group receiving treatment with chlorthalidone as the primary drug, 1.6%. However, according to a later more detailed evaluation,[40] a differential dropout and loss of data from participants in the placebo- and actively treated groups may well have biased the analysis of cognitive effects of active treatment and, hence, obscured a protective action of the antihypertensive regimen.

In the Perindopril Protection against Recurrent Stroke Study,[41] the ACE inhibitor perindopril failed to prevent poststroke dementia. However, in combination with the diuretic

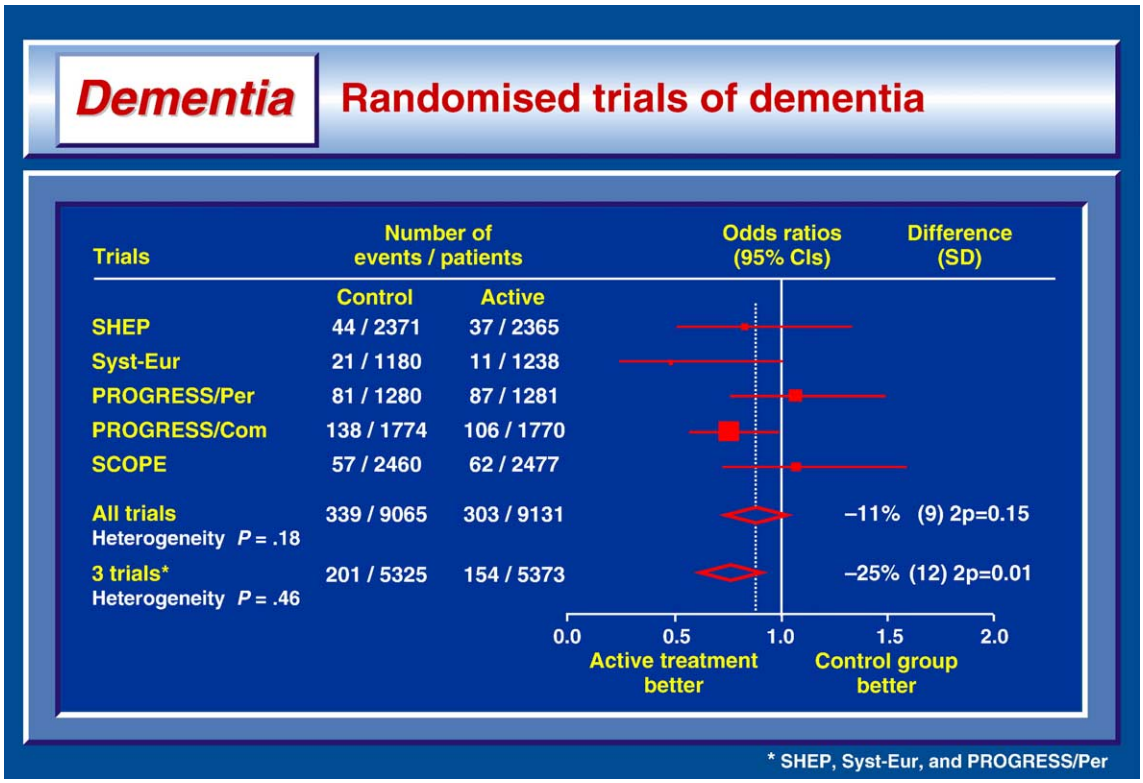

Fig 3. Meta-analysis of randomized antihypertensive dementia prevention studies. Reprinted with permission from *Semin in Cerebrovasc Dis Stroke* 2003;3:155-160.

indapamide, a 23% reduction (P = .05) in the incidence of dementia was observed.

The Study on Cognition and Prognosis in the Elderly[42] tested the protective effect of the AT1-blocker candesartan against placebo. As to the latter group, it should be noted that 80% of patients on "placebo" actually received a diuretic for ethical reasons. Small wonder that this procedure actually invalidated the trial results, which failed to demonstrate any protective effect of candesartan on dementia.

The Syst-Eur trial included a side project investigating, in a double-blind fashion, the incidence of dementia in 2418 subjects 60 years and older with systolic hypertension.[43] The basic treatment consisted of the CCB nitrendipine vs matching placebo as primary drug, with enalapril and hydrochlorothiazide and their matched placebos as complementary medication when considered to be necessary. The median follow-up lasted only 2 years because of a critical difference between stroke rates in the actively and placebo-treated groups. Active treatment reduced dementia by 50% from 7.7 to 3.8 per 1000 observation years in stroke-free subjects. After the close of the double-blind period, it was decided, for ethical reasons, to offer all patients, including those in the former placebo group, the active form of trial medication for an extended period.

This move, designated as Syst-Eur 2, doubled the observation period in an open fashion.[44] As indicated in Fig 1, in the course of the latter period, BPs approached identity in the earlier placebo- and actively treated patients.[45] Nevertheless, the latter, as indicated in Fig 2, still exhibited a relative profit in avoiding or at least retarding the development of dementia (−55%, $P < .001$).[45]

Altogether, the combination of the above 4 trials would seem to offer only a slim profit of antihypertensive treatment for preventing dementia: as indicated in Fig. 3, the overall odds ratio was 0.89 (95% CI, 0.75-1.04).[46] Exclusion of drugs affecting the renin-angiotensin system (perindopril without indapamide and candesartan) would lead to a more promising pooled odds ratio (0.75; 95% CI, 0.60-0.94).[46] Despite its small numbers, the double-blind phase of the Syst-Eur trial,[43] because of its primary drug nitrendipine, apparently carried the best message of preventing dementia (Fig 3).

Discussion

Dementia (whether diagnosed as being vascular or degenerative), because of increasing somatic longevity of the elderly population, looms ahead as an epidemic of catastrophic proportions. This will occur in the aging population at large but apparently even more so in hypertensive patients. Although hypertensive target organ damage, in general, may be attenuated through adequate treatment with all currently available antihypertensive drugs, cognitive deterioration seems to be quite resistant to such routine treatment, as indicated above. Our favorable experience in the Syst-Eur trial, with a dihydropyridine CCB as the primary drug, is tempting us to recommend this class of antihypertensives for the prevention of both types of overt dementia, provided that the reduction in BP remains within reasonable limits for this age group, as indicated in Fig 1.

Some studies seemed to be at variance with our findings, but both were retrospective and confounded by indication, in the sense that CCBs were favored for high-risk patients.[47,48] This is a particularly disturbing feature of the interpretation of treatment results of CCBs.[49]

Several better-organized, prospective studies (although not in a properly randomized, placebo-controlled fashion), resulted in statistically significant favorable effects of the dihydropyridine CCB nimodipine on containing mental deterioration[50] and borderline significant protection by dihydropyridine CCBs as a drug class.[51]

From a conceptual point of view, this clinically established capacity of dihydropyridine CCBs would be quite plausible. First of all, according to in vitro and in vivo experimental evidence, intracellular free calcium accumulation plays a dominant role in age-related deterioration of a cascade of cerebrocellular functions, which are critically involved in brain aging, sensitization to neurotoxins, and cell death.[52-56] Secondly, the distribution of action of dihydropyridine CCBs (nitrendipine and nicardipine) has been shown to focus on areas in the rat brain corresponding to the human target cerebral areas involved in the development of dementias.[57,58]

Because the circle of evidence regarding the efficacy of the dihydropyridine class of CCBs in preventing/retarding the incidence of both types of dementia has virtually been closed, one can

hardly forfeit the conclusion that such agents should at least be an ingredient of any hypertensive regimen for individuals older than 60 years or, perhaps, even younger given recent findings.[23]

We have argued repeatedly that there remains an urgent need for further long-term randomized comparative trials in hypertensive patients encompassing the current main classes of antihypertensive drugs, tailored to equal BPs and focusing on exponents of cognition.[14,59] The recently published Anti-hypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial[60] and Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm[61] trials could have fulfilled this purpose, if only the organizers would have monitored equal BPs more closely and included proper attention to the course of cognitive aspects in relation to the courses of BP.

This leaves investigators involved in clinical hypertension with the moral duty to organize still another comparative prospective treatment trial including assessment of the cognitive status as a necessary ingredient of end point evaluation.

References

1. Hofman A, Ott A, Breteler MM, et al: Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 349:151-154, 1997
2. Casserly I, Topol E: Convergence of atherosclerosis and Alzheimer's disease: Inflammation, cholesterol, and misfolded proteins. Lancet 363:1139-1146, 2004
3. Neuropathology Group Medical Research Council Cognitive Function and Aging Study: Pathological correlation of late-onset dementia in a multicentre, community-based population in England and Wales. Lancet 357:169-175, 2001
4. Barker A, Jones R, Jennison C, et al: A prevalence study of age-associated memory impairment. Br J Psychiatry 167:642-648, 1995
5. Coria F, Gomez de Caso JA, Minguez L, et al: Prevalence of age-associated memory impairment and dementia in a rural community. J Neurol Neurosurg Psychiatry 56:973-976, 1993
6. Larrabee GJ, Crook TH: Estimated prevalence of age-associated memory impairment derived from standardized tests of memory function. Int Psychogeriatr 6:95-104, 1994
7. Rocca WA, Bonaiuto S, Lippi A: Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: A door-to-door survey in Appigano macerata Province, Italy. Neurology 40:626-631, 1990
8. Canadian Study of Health and Aging Working Group: Canadian Study of Health and Aging: Study methods and prevalence of dementia. Can Med Assoc J 150:899-913, 1994
9. Ernst R, Hay JW: The US economic and social costs of Alzheimer's disease revisited. Am J Public Health 84:1261-1264, 1994
10. Fratiglioni L, De Ronchi D, Aguero-Torres H: Worldwide prevalence and incidence of dementia. Drugs Aging 15:365-375, 1999
11. Brookmeyer R, Gray S, Kawas C: Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 88:1337-1342, 1998
12. Courtney C, Farrell D, Gray R, et al: D2000 Collaborative Group: Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): Randomised double-blind trial. Lancet 363:2005-2115, 2004
13. Rigaud AS, Seux ML, Staessen JA, et al: Cerebral complications of hypertension. J Hum Hypertens 14:605-616, 2000
14. Birkenhäger WH, Forette F, Seux ML, et al: Blood pressure, cognitive functions, and prevention of dementias in older patients with hypertension. Arch Intern Med 161:152-156, 2001
15. Skoog I: Detection of preclinical Alzheimer's disease. N Engl J Med 343:502-503, 2000
16. Scahill RI, Schott JM, Stevens JM, et al: Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered MRI. Proc Natl Acad Sci U S A 99:4703-4707, 2002
17. Elias ME, Wolf PA, D'Agostino RB, et al: Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. Am J Epidemiol 138:353-364, 1993
18. Skoog I, Lernfelt B, Landahl S, et al: A 15-year longitudinal study of blood pressure and dementia. Lancet 347:1141-1145, 1996
19. Kilander L, Nyman H, Boberg M, et al: Hypertension is related to cognitive impairment: A 20-year follow-up study of 999 men. Hypertension 31:780-786, 1998
20. Launer LJ, Ross GW, Petrovich H, et al: Midlife blood pressure and dementia: The Honolulu-Asia aging study. Neurobiol Aging 21:49-55, 2000
21. Skoog I: Blood pressure and dementia, in Hansson L, Birkenhäger WH, (Eds.): Assessment of hypertensive organ damage. Handbook of Hypertension, vol. 18, Amsterdam, Elsevier Science, 1997, pp. 303-331
22. De la Torre JC: Alzheimer disease as a vascular disorder: Nosological evidence. Stroke 33:1152-1162, 2002
23. Elias PK, Elias MF, Robbins MA, et al: Blood-pressure related cognitive decline: Does age make a difference? Hypertension 44:631-636, 2004
24. Chobanian AV, Bakris GL, Black BK, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42:1206-1252, 2003
25. Schmidt R, Enzinger C, Ropele S, et al: Progression of cerebral white matter lesions: 6-year results of the

Austrian stroke prevention study. Lancet 361:2046-2048, 2003
26. Geroldi C, Galluzi S, Testa C, et al: Validation study of a CT-based weighted rating scale for subcortical ischemic vascular disease in patients with mild cognitive deterioration. Eur Neurol 49:193-209, 2003
27. Dufouil C, de Kersaint-Gilly A, Besancon V, et al: Longitudinal study of blood pressure and white matter hyperintensities. The EVA MRI cohort. Neurolgy 56:921-926, 2001
28. De Leeuw FE, De Groot JC, Oudkerk M, et al: Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 125:765-772, 2002
29. Van Dijk EJ, Breteler MMB, Schmidt R, et al: for the CASCADE Consortium: The association between blood pressure, hypertension and cerebral white matter lesions: The CASCADE study. Hypertension 44:625-630, 2004
30. Staessen JA, Gasowski J, Wang J-G, et al: Risks of untreated and treated isolated systolic hypertension in the elderly. Lancet 355:865-872, 2000
31. Guo Z, Fratiglioni L, Zhu L, et al: Occurrence and progression of dementia in a community population aged 75 years and older: Relationship of antihypertensive medication use. Arch Neurol 56:991-996, 1999
32. Qiu C, Von Strauss E, Fastbom J, et al: Low blood pressure and risk of dementia in the Kungsholmen project: A 6-year follow-up study. Arch Neurol 60: 223-228, 2003
33. Tzourio C, Dufouil C, Ducimetiere P, et al: Cognitive decline in individuals with high blood pressure. Neurology 53:1948-1952, 1999
34. Prince MJ, Bird AS, Blizard, et al: Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. BMJ 312:801-805, 1996
35. Glynn RJ, Becket LA, Herbert LE, et al: Current and remote blood pressure and cognitive decline. JAMA 281:438-445, 1999
36. Kipivelto M, Helkala EL, Haanninen T, et al: Midlife vascular risk factors and late-midlife cognitive impairment: A population study. Neurology 56:1683-1689, 2001
37. Paran E, Anson O, Reuveni H: Blood pressure and cognitive functioning among independent elderly. AJH 16:818-826, 2003
38. Murray MD, Lane KA, Gao S, et al: Preservation of cognitive function with antihypertensive medications: A longitudinal analysis of a community-based sample of African Americans. Arch Intern Med 162:2090-2096, 2002
39. Applegate WB, Pressel S, Wittes J, et al: Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 154: 2154-2160, 1994
40. DiBari M, Pahor M, Franse LV, et al: Dementia and disability outcomes in large hypertension trials: Lessons learned from the Systolic Hypertension in the Elderly Program (SHEP) trial. Am J Epidemiol 153: 72-78, 2001
41. The PROGRESS Collaborative Group: Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cardiovascular disease. Arch Intern Med 163:1069-1075, 2003
42. Lithell H, Hansson L, Skoog I, et al: The Study on Cognition and Prognosis in the Elderly (SCOPE): Principal results of a randomized double-blind intervention trial. J Hypertens 21:875-886, 2003
43. Forette F, Seux ML, Staessen JA, et al: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 352:1347-1351, 1998
44. Staessen JA, Thijs L, Fagard R, et al: Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. J Hypertens 22:847-857, 2004
45. Forette F, Seux ML, Staessen JA, et al: The prevention of dementia with antihypertensive treatment: New evidence from the Systolic Hypertension in Europe (Syst-Eur) Study. Arch Intern Med 162: 2046-2052, 2002
46. Wang J-G, Staessen JA, Birkenhäger WH: Antihypertensive treatment and prevention of stroke and dementia. Semin in Cerebrovasc Dis Stroke 3: 155-160, 2003
47. Heckbert SR, Longstreth WT, Psaty BM, et al: The association of antihypertensive agents with MRI white matter findings and with modified Mini-Mental State Examinations in older adults. J Am Geriatr Soc 45:1423-1433, 1997
48. Maxwell CJ, Hogan JB, Ebly EM: Calcium channel blockers and cognitive function in elderly people: Results from the Canadian Study of Health and Aging. CMAJ 161:501-506, 1999
49. Leader S, Rohr L: Evidence of confounding by indications: Prescribing of calcium antagonists. Am J Hypertens 12:26A-27A, 1999
50. Morich FJ, Bieber F, Lewis JM, et al: Nimodipine in the treatment of probable Alzheimer's disease. Results of two multicenter trials. Clin Drug Invest 11:185-195, 1996
51. Jasar S, Corrada M, Brookmeyer R, et al: Calcium channel blockers and the risk of AD: The Baltimore Longitudinal Study of Aging. Neurobiol Aging 2004 [in press]
52. Khachaturian Z: Calcium, membranes, aging. Ann NY Acad Sci 568:1-4, 1989
53. Thibault O, Porter MM, Chen KC: Calcium dysregulation in neuronal aging and Alzheimer's disease: History and new directions. Ceeel Calcium 25:417-433, 1998
54. Pascale A, Etcheberrigaray R: Calcium alterations in Alzheimer's disease: Pathophysiology, models, and therapeutic opportunities. Pharmacol Res 39:81-88, 1999
55. LaPerla F: Calcium dyshomeostasis and intracellular signaling in Alzheimer's disease. Nat Rev Neurosci 3:862-872, 2002

56. Zipfel GJ, Lee IM, Choi DW: Reducing calcium overload in the ischemic brain. N Engl J Med 341: 1543-1544, 1999

57. Gould RJ, Murphy KMM, Snyder SH: Autoradiographic localization of calcium channel antagonist receptors in rat brain with [3H] nitrendipine. Brain Res 330:217-223, 1985

58. Amenta F, Strocchi P, Sabbatini M: Vascular and neuronal brain damage: Protective effect of treatment with nicardipine. J Hypertens S29-S36, 1996 (Suppl 3)

59. Birkenhäger WH, Forette F, Staessen JA: Dementia and antihypertensive treatment. Curr Opin Nephrol Hypertens 13:225-230, 2004

60. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Anti-hypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 288:2981-2997, 2002

61. Dahlöf B, Sever PS, Poulter NL: for the ASCOT investigators: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol, adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. Lancet 366: 895-906, 2005